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Exploring the relationship between depression and vitamin D supplementation in vitamin D deficient and insufficient patients: Review of the literature

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ABSTRACT

Aim: We conducted this review of the literature to assess the available knowledge on vitamin D supplementation in vitamin D deficient and insufficient patients suffering from depression. *Methods:* We used the PubMed database to search for the articles. After applying the inclusion criteria, we selected ten eligible articles. We presented our results in two forms, a table and a summary, containing crucial information about each article. *Results:* Out of the ten articles, five supported the positive effect of vitamin D supplementation on depression severity; five of them were against it, although in some positive relationships between other indices, for example, anxiety severity, were described. *Limitations:* The major limitation of the articles we investigated was the relatively small sample size; in most articles, less than 70 participants completed the study. Moreover, different authors used different standardized rating scales of depression; in total, five scales were used; thus, it could impact the comparability of the results. Not all patients that were supplementing vitamin D reached the threshold of vitamin D sufficiency; hence, further research should consider ending the trial not at a set time but after all the participants receiving the intervention would become vitamin D sufficient. *Conclusions:* The literature remains equivocal about the investigated topic. Further research needs to be conducted to investigate the effect of supplementing vitamin D in vitamin D deficient and insufficient patients suffering from depression.

Keywords: Vitamin D deficiency; vitamin D insufficiency; vitamin D supplementation; depression; major depressive disorder.

1. INTRODUCTION

Depression

Depressive disorders – dysthymia and major depressive disorder (MDD), are one of the two most common mental disorders; the other one is anxiety disorder (Ferrari et al., 2019). The Global Burden of Disease Study 2019 reported that the prevalence of depressive disorders is 280 million, with 100 million suffering from dysthymia and 185 million suffering from MDD; in all of them, women comprise a greater percentage, about 61% of all depressive disorders. In 2020, the prevalence of MDD increased significantly to 246 million, with an estimated 53.2 million additional cases due to the COVID-19 pandemic COVID-19 Mental Disorders Collaborators, (2021), about a 33% increase in just one year. In contrast to those numbers, in 2000, the prevalence of depressive disorders was 170.8 million, with 71 million suffering from dysthymia and 145 million suffering from MDD.

Data provided by Eurostat (2021) shows that in 2019, 7.2% of the European Union (EU) population aged 15 years or older had chronic depression. In the USA, in 2020, the reported estimated prevalence of depression in adults aged ≥18 years was 18.4% or 47 million (Lee et al., 2020). Depressive disorders can greatly impact an individual's life. It is estimated that they can account for 46.8 million disability-adjusted life years (DALYs), and in 2019, they were ranked 13th among leading causes of DALYs (Ferrari et al., 2019; GBD 2019). The extent of the data provided shows that depression is one of the most alarming issues healthcare professionals face today. The awareness and links between different factors impacting the incidence of this disorder should be thoroughly studied.

Moreover, considering the state of the world, the socio-economic challenges people experience today, the aftermath of the COVID-19 pandemic, and many other factors, there is a high possibility that the incidence of depression will continue to increase. The underlying pathophysiology of depression to this day remains not entirely elucidated. One of the most influential hypotheses is the brain's chemical imbalance, namely lower serotonin levels, which the first mentions can be traced back to 1960 (Coppen, 1967). More recent studies suggest that the chemical imbalance theory may not be valid and that the antidepressants themself may not be as effective as they were thought to be, with adverse effects outweighing the benefits (Moncrieff et al., 2023; Jakobsen et al., 2020). Some studies suggest that even up to 68% of patients starting with antidepressants stop taking them within three months and their side effects may play a crucial role in this phenomenon; moreover, up to 54% of patients do not reach remission (Anderson et al., 2012; Lin et al., 1995; Maddox et al., 1994; Bull et al., 2002).

Vitamin D deficiency

Vitamin D is a vital steroidal hormone, essential for the proper and adequate functioning of the human body (Vandikas et al., 2022; Bikle and Christakos, 2020). Its synthesis begins in epidermis, where through a reaction facilitated by ultraviolet B (UVB) radiation 7-dehydrocholesterol is transformed into cholecalciferol; then it undergoes hydroxylation in the liver and the kidneys, and the final product, biologically active calcitriol (1,25-dihydroxycholecalciferol), is obtained (Bhattacharyya and DeLuca, 1974; Zhu et al., 2013; Bikle et al., 2018). Calcitriol mainly acts via its specific vitamin D nuclear receptor (VDR), regulating the expression of many genes (Khammissa et al., 2018). Its functions involve intestinal calcium absorption, renal calcium and phosphate reabsorption, bone metabolism and homeostasis, proliferation and differentiation of different cell lines, immune system regulation, and many more (Khammissa et al., 2018; Christakos et al., 2016). Vitamin D deficiency is differently defined by various sources.

The Endocrine Society defines vitamin D deficiency as serum concentrations < 20 ng/ml (50 nmol/L), 20-29 ng/ml (52.5-72.5 nmol/L) is insufficiency and sufficiency is > 30 ng/ml (75 nmol/L) (Basińska-Lewandowska et al., 2021). It is estimated that globally 47.9% and 76.6% of people suffer from vitamin D deficiency and insufficiency, respectively (Cui et al., 2023). Vitamin D deficiency can lead to many impairments, including osteomalacia, fractures, muscle weakness, diabetes, multiple sclerosis, hypertension, metabolic syndrome, cancers, autoimmune diseases, and cardiovascular diseases (Cui et al., 2023; Holick, 2007; Autier et al., 2014; Costenbader, 2022; Zhou et al., 2022; Mailhot and White, 2020).

The vital role of vitamin D in regulating calcium homeostasis is well known. Nonetheless, vitamin D receptors have been found in the brain; some researchers call vitamin D neurosteroid as it is vital to many processes in the brain and its deficiency can lead to numerous neuropsychiatric disorders; early on in life, for example, schizophrenia or when present later in life - Alzheimer's disease, Parkinson's disease, depression and cognitive impairments (Kesby et al., 2011). Moreover, vitamin D, by activating transcription of

tryptophan hydroxylase 2, plays an essential role in serotonin synthesis; hence, vitamin D deficiency may lead to insufficient serotonin production in the brain (Patrick and Ames, 2014; Patrick and Ames, 2015).

2. METHODS

The inclusion criteria we developed for the review were as follows:

-Clinical trial or randomized controlled trial,

-Articles published during or after 2014,

-Age or mean age of enrolled patients between 18 to 65 years,

-Excluding pregnant women and postpartum depression,

-Plasma vitamin D concentration at baseline <30 ng/ml (equal to <75 nmol/l) Basińska-Lewandowska et al., (2021),

-Depression assessed using standardized depression rating scales: Beck's Depression Inventory (BDI), Beck's Depression Inventory II (BDI-II), Hamilton Depression Rating Scale (HDRS/HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), The Center for Epidemiologic Studies Depression Scale (CES-D),

-Patients in the trial had to suffer from depression: BDI >9, BDI-II >13, HAM-D >7, MADRS >6, CES-D >15, (Zelter, 2008; Sharp, 2015; National Library of Medicine, 2016; Radloff, 1977),

-Only vitamin D was supplemented, not in conjunction with other substances, for example, omega-3 fatty acids (use of antidepressants was not a criterion for exclusion of an article).

Screening for the articles was conducted until 5th April 2024. This review used the PubMed database to search for the articles. The keywords that we used were “vitamin D deficiency” and “depression”. We decided to use “vitamin D deficiency” instead of “vitamin D insufficiency”, as “insufficiency” yielded significantly fewer articles after applying filters (11 instead of 44 articles) and potentially eligible articles from this search were also present in the “deficiency” search. The keywords used in PubMed yielded 745 articles; after applying filters, “clinical trials”, and “randomized controlled trial”, and published between 2014-2024, PubMed yielded 44 articles. Excluding articles that did not meet the inclusion criteria, we selected ten articles. The selection process is visually presented in (Figure 1). The article selection process was conducted by Marcin Głód and Marta Węgrzynek. This systemic review was written and structured using the following guidelines: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for 2020 (PRISMA).

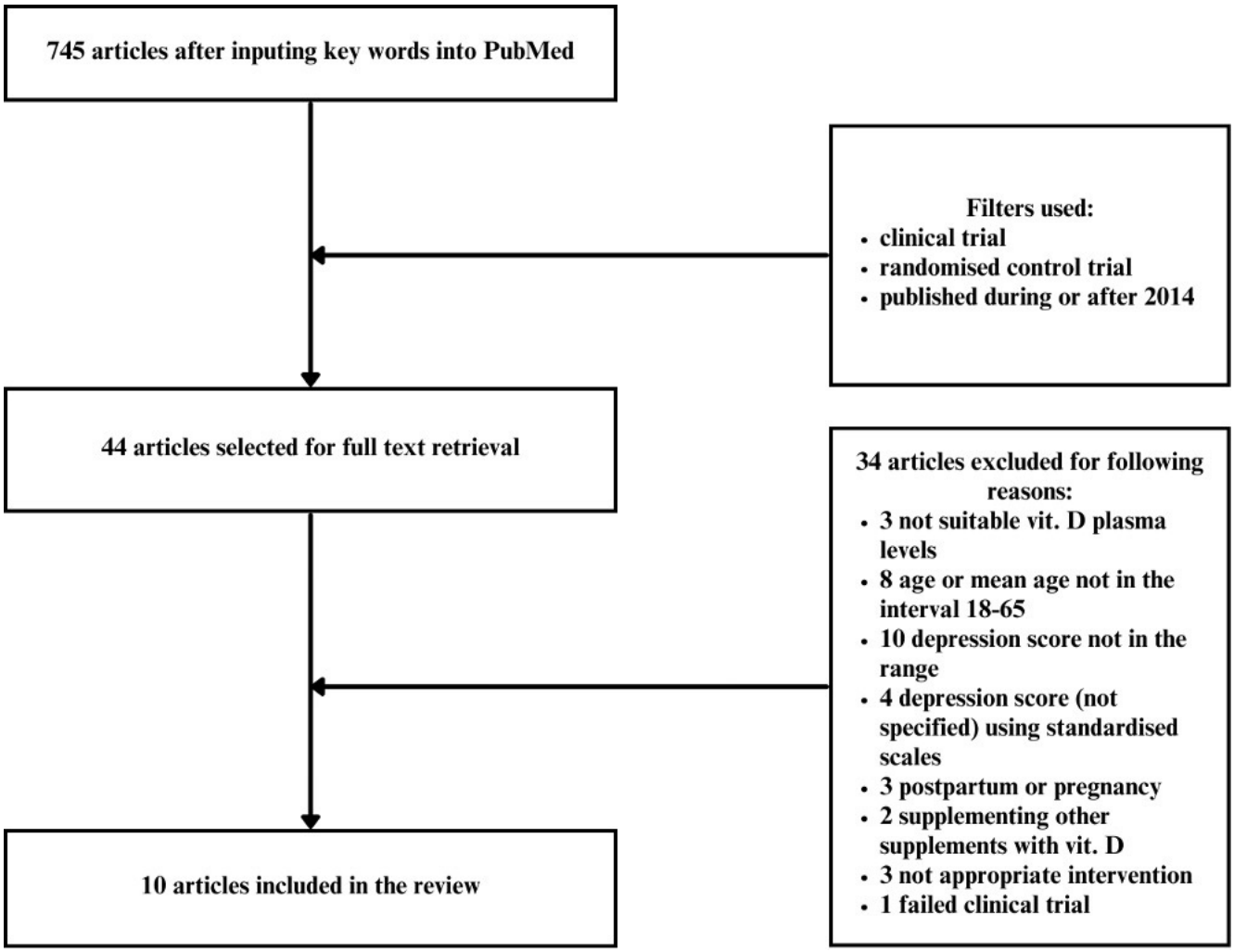

Figure 1 Flow chart detailing the process of selecting eligible articles.

3. RESULTS

Study selection

As aforementioned, after applying the inclusion criteria, we selected ten studies. 34 articles did not meet the inclusion criteria; examples of them are listed below:

-Studies that supplemented vitamin D in conjunction with other substances, for example, omega-3 Rajabi-Naeeni et al., (2021),

-Studies where no vitamin D was supplemented, but sun exposure and outdoor activity were promoted Thomas and Al-Anouti, (2018),

-Studies where most of the participants had vitamin D sufficiency or vitamin D levels that were above the levels we set as the inclusion criteria Sharifi et al., (2019),

-Studies where patients had vitamin D deficiency, but standardized rating scales of depression were under the threshold, implicating that a patient may not suffer from depression Mousa et al., (2018),

-Not appropriate intervention Karacin et al., (2018),

-Studies where the age of the individuals enrolled were under or above the interval 18-65 years old (Alavi et al., 2019; Libuda et al., 2020).

Study characteristics

We decided that a preliminary data presentation in the form of a table would be more comprehensible and would facilitate a comparison of the ten articles we selected for this review. To avoid hindering effective comparison, we aimed to limit the data

presented in the table 1, as showing 20 or more variables detailing each article would not be beneficial for effective data assessment. Each study will be described by:

Column 2 - n - number of patients that received the intervention and completed the follow-up,

Column 3 - mean baseline vitamin D plasma concentration in the intervention group, the units used are ng/ml; if authors used nmol/L, the results were converted into ng/ml; 1 nmol/L = 0.4 ng/ml (National Institutes of Health, 2023),

Column 4 - mean final vitamin D plasma concentration in the intervention group (if the absolute value was not specified by the authors, we used "+" as an increase by stated value),

Column 5 - due to different standardized rating scales of depression, the change in depression severity is complicated to show in the table; hence, we decided that "yes" and "no" would suffice, which implies the intervention was or was not successful in improving depression severity, respectively.

Table 1 Preliminary data of the selected articles.

	n	Baseline vit. D	Final vit. D	Endpoint
Vellekkatt et al., 2020	42	< 20	Not measured	Yes
Bagheri et al., 2022	46	23.3 ± 10.5	25.6 ± 10.1	Yes
Omidian et al., 2019	66	15.5 ± 8.8	+ 16.9 ± 5.9	Yes
Ghaderi et al., 2017	60	13.9 ± 4.5	22.0 ± 7.5	Yes
Ghaderi et al., 2020	64	14.1 ± 4.2	27.5 ± 4.2	Yes
Zhu et al., 2020	106	15.6 ± 4.2	Not specified	No
Marsh et al., 2017	25	19.2 ± 5.8	+ 9.9 ± 8.2	No
Kumar et al., 2022	41	11.6 ± 2.6	77.9 ± 40.6	No
Hansen et al., 2019	45	17.3 ± 9.8	39.2 ± 10.0	No
Torrisi et al., 2021	40	19.6 ± 7.9	± 6.4	No

From ten selected articles, five articles provided data that suggest that supplementing vitamin D in vitamin D deficient patients could yield positive results in depression severity. Five articles provided data that supplementing vitamin D did not yield satisfactory results in comparison with the control.

Articles in favor of a positive relationship between vitamin D supplementation and depression severity

As aforementioned five articles provided data suggesting that supplementing vitamin D in vitamin D deficient patients could improve depression severity. The doses of vitamin D administered varied across studies. In some 50,000 IU orally was administered every two weeks Bagheri et al., (2022), Ghaderi et al., (2017), Ghaderi et al., (2020), 4,000 IU orally daily Omidian et al., (2019) or one injection intramuscularly in the gluteal region of 300,000 IU cholecalciferol was used to maximize compliance (Vellekkatt et al., 2020). In all trials mentioned here, vitamin D levels increased from baseline to the end of the trial, but in some, the threshold of adequate vitamin D level (30 ng/ml) was not reached.

Vellekkatt et al., (2020) in their trial injected 300,000 IU of cholecalciferol as an intervention for patients suffering from MDD; the number of patients that completed follow-up was 42 (46 patients were analyzed), and their mean age was 35.9 ± 11.6 years. Before the trial, patients were not on antidepressant drugs, but both groups were initiated on them at the start of the trial. The authors did not provide mean vitamin D plasma levels at the baseline (only that the inclusion criterion was serum 25-hydroxyvitamin D level < 20 ng/ml) and after the intervention, so we cannot assess whether, after supplementing vitamin D, participants were or were not still vitamin D deficient. There were no major side effects of the intervention reported by enrolled patients. The depression severity was assessed using HAM-D. The change from baseline to the 12th week of follow-up was 19.4 ± 4.0 to 3.0 (2.0–4.0) in the intervention group and 17.44 ± 3.1 to 5.0 (3.2–8.0) in the control group.

The p-value of the difference between the intervention and control group of HAM-D score at the 12th-week follow-up was equal to 0.001, implying that the difference is statistically significant. Furthermore, the authors reported that the secondary outcomes, quality of life, and clinical severity of illness improved significantly; the differences at the 12th week of the follow-up were statistically significant

comparing the intervention to the control group with $p < 0.001$ in both indices. Bagheri et al., (2022) studied the effect of supplementing 50,000 IU of vitamin D every two weeks for 24 weeks. The final analysis comprised 46 tobacco-misusing patients who completed follow-up, 24 in the intervention group and 22 in the control group. The mean age of the participants was 35.4 ± 12.8 years for the intervention group and 34.9 ± 12.3 for the placebo. The intervention increased vitamin D levels from baseline to week 24, from 23.3 ± 10.5 ng/ml to 25.6 ± 10.1 ng/ml; the p-value of the difference in vitamin D plasma levels at the 24th week between the intervention and control groups was equal to 0.006.

Most of the patients were still vitamin D insufficient at the end of the intervention. The mean BDI score of the intervention group decreased from 25.8 ± 10.2 to 23.0 ± 10.7, while the control group's mean BDI score changed from 26.4 ± 11.7 to 25.6 ± 11.5; compared with the control group, the difference in BDI score at week 24 was deemed statistically significant with $p = 0.02$. In this trial, alongside depression severity, the anxiety was assessed using the Beck Anxiety Inventory (BAI); the mean BAI score in the intervention group decreased from baseline to week 24, from 19.6 ± 10.2 to 18.1 ± 9.7, respectively; in the control group BAI changed from 22.0 ± 9.3 to 21.5 ± 8.5; the p-value for difference in outcome measures between vitamin D and placebo treatment groups was 0.08, deeming it statistically insignificant. The authors did not provide data on whether participants were or were not taking antidepressant drugs, which could skewer the results of the trial. Researchers reported no side effects after the administration of vitamin D.

Omidian et al., (2019), in their trial, administered daily 4,000 IU of vitamin D for 12 weeks to patients suffering from type 2 diabetes and mild to moderate depression; 66 participants completed the study. The mean age of the intervention group was 49.7 ± 6.5 years, and of the placebo group was 51.3 ± 5.9 years. Patients in this study were not using antidepressants either before the study or during it. Mean 25-hydroxyvitamin D serum concentrations were < 20 ng/ml at the baseline. The mean change in vitamin D level at baseline vs. at the end of the trial was significantly different for the intervention group vs. placebo, 16.9 ± 5.9 ng/ml and 0.8 ± 4.3 ng/ml, respectively, with p-value < 0.001. Unfortunately, vitamin D levels at the end of the follow-up are not stated, so we cannot evaluate whether patients in the intervention group were still vitamin D deficient or insufficient at the end of the trial.

Supplementing vitamin D improved depression severity, BDI-II scores decreased by 27.5% (5.4) in the intervention group, while in the placebo group, BDI-II scores decreased by 10.8% (1.8) with p-value = 0.02, deeming this difference statistically significant. Furthermore, the authors reported that supplementing vitamin D significantly decreased HbA1c, insulin, and triglyceride levels. Researchers did not provide information on whether any side effects of vitamin D supplementation occurred. Ghaderi et al., (2017) and Ghaderi et al., (2020) conducted two trials where every two weeks, they administered 50,000 IU of vitamin D orally for 12 weeks in 2017 and 24 weeks in 2019 as an intervention to patients undergoing methadone maintenance treatment.

The sample sizes of the trials were similar; the number of patients that completed the trial and follow-up in 2017 was 60 patients (mean age 40.1 ± 9.2 years for the intervention and 42.5 ± 8.9 years for the placebo group), and in 2019 it was 64 patients (mean age 37.5 ± 10.8 years for the intervention and 40.8 ± 9.5 years for the placebo group). The intervention yielded a significant increase in vitamin D concentration and improved the severity of depression by decreasing the BDI score. In 2017, vitamin D plasma levels increased from 13.9 ± 4.5 ng/ml to 22.0 ± 7.5 ng/ml with a p-value < 0.001 in comparison with the control. The BDI score of the intervention group decreased from 22.3 ± 6.1 to 17.4 ± 6.0, while for the control group, it decreased from 22.3 ± 6.1 to 21.5 ± 6.7, with $p = 0.04$ for the difference between the intervention and control group at the endpoint.

Furthermore, in 2017, researchers described improvement in Pittsburgh Sleep Quality Index (PSQI), glycemic control, hs-CRP, total antioxidant capacity (TAC), total glutathione (GSH), and lipid profiles except for HDL, and after adjusting for some variables, BAI score also improved in the intervention group. In 2019, vitamin D plasma levels increased from 14.1 ± 4.2 ng/ml to 27.5 ± 4.2 ng/ml, the p-value < 0.001 in comparison with the control, the BDI score in the intervention group decreased from 14.8 ± 5.6 to 12.7 ± 4.6, and in the control group, it increased from 15.9 ± 4.4 to 16.1 ± 2.9, with $p < 0.001$ between intervention and baseline at 24th week. In the study from 2017, the authors did not state if any side effects were reported, but in the study from 2019, they stated that no adverse reactions were reported following vitamin D consumption.

Articles against positive relationship between vitamin D supplementation and depression

Zhu et al., (2020) decided to daily supplement orally 1,600 IU of vitamin D for six months as an intervention for patients diagnosed with MDD. The mean age of the participants for the intervention and control group was 46.3 ± 9.7 years and 43.3 ± 13.7 years, respectively. At the endpoint, 62 patients were in the intervention group and 44 in the control group. Out of 106 patients, only 11 were not using antipsychotics. Patients were vitamin D deficient with plasma levels < 20 ng/ml. Mean vitamin D serum levels in the

intervention group were 15.6 ± 4.2 ng/ml and for the control group were 16.8 ± 5.0 ng/ml. Researchers did not provide data on how vitamin D levels changed throughout the trial. The baseline levels of depression severity measured by HAM-D score were 30.0 ± 7.6 for the intervention and 29.2 ± 11.6 for the control group.

The authors did not provide exact numbers on how the HAM-D score changed during the 3rd and 6th months of the follow-up (only a linear chart is provided, which hinders the accurate retrieval of data). They reported that the HAM-D score between the intervention and control group did not differ with p-value > 0.05, suggesting that vitamin D intervention was not beneficial for improving depression severity. Authors, besides depression severity, measured other outcomes, including the Revised Social Anhedonia Scale (RSAS), Revised Physical Anhedonia Scale (RPAS), and Hamilton Anxiety Rating Scale-14 (HAM-A). They reported that at the 6th month of follow-up, the differences between the intervention and the control groups in scores of RSAS and RPAS were not statistically significant.

However, there was a significant decrease in HAM-A score between investigated groups at the 6th month - intervention group 8.502 ± 0.483 (from 18.0 ± 5.7) versus control group 7.245 ± 0.402 (from 17.9 ± 7.5) with p = 0.041. The authors did not explain whether adverse reactions after supplementing vitamin D occurred. Marsh et al., (2017) orally administered 5,000 IU of vitamin D daily for 12 weeks. Patients enrolled were suffering from bipolar depression and experiencing mild or greater depressive symptoms on the MADRS scale (>7). The mean age was 45.2 ± 13.3 years for the intervention group and 43.3 ± 12.9 years for the placebo group. 25 patients completed the trial, 13 in the intervention and 12 in the placebo group. Most of the patients were on psychotropic medications, but the authors stated that there was no statistically significant difference between the investigated groups.

Mean vitamin D serum levels were 19.2 ± 5.8 ng/ml for the intervention group and 19.3 ± 5.5 ng/ml for the placebo group; after 12 weeks of intervention, it increased by 9.9 ± 8.2 ng/ml in the intervention group, and by 1.3 ± 4.3 ng/ml in the placebo group. Five (31.3%) patients from the intervention group and one patient from the control group reached levels > 30 ng/ml. Mean MADRS scores at the baseline were 21.3 ± 6.4 for the intervention and 22.8 ± 6.9 for the control group. In both groups, they decreased during the trial, in the intervention to 9.54 and in the placebo group to 6.42; however, the p-value of the difference between groups was equal to 0.89, deeming it statistically insignificant. As aforementioned, in the trial by Zhu et al., (2020), researchers reported positive effects of supplementing vitamin D on anxiety symptoms.

In this trial, the HAM-A significantly decreased in both groups, however, the difference was deemed not statistically significant with p = 0.92. No serious adverse events were reported. Kumar et al., (2022) recruited patients with vitamin D deficiency, MDD without psychotic features, HAM-D score ≥ 15, and who were not using antidepressants or antipsychotic drugs two months before the trial. The mean age of the intervention group was 34.9 ± 10.5 years, and the control group was 39.3 ± 11.8 years (the mean age of the randomized sample was 36.8 ± 11.3 years). The number of analyzed patients was 59, but 18 were lost to follow-up. As an intervention, 60,000 IU of cholecalciferol was chosen every five days for 12 weeks. The authors initiated all patients on escitalopram 10 mg/day, which was titrated up to a maximum of 20 mg/day.

Also, oral clonazepam was administered to some patients reporting insomnia or anxiety (maximum dose 2 mg/day). Vitamin D plasma levels in the intervention group increased from 11.6 ± 2.6 ng/ml to 77.9 ± 40.6 ng/ml at 12th week, whereas in the control group, it increased from 11.4 ± 3.3 ng/ml to 33.6 ± 41.2 ng/ml; the p-value for the difference in vitamin D plasma concentration between the intervention and the control group at 12th week was p = 0.008. The HAM-D score in the intervention group decreased from baseline 25.7 ± 8.0 to 5.7 ± 6.9 in the 12th week; in the control group, it decreased from 25.8 ± 10.3 to 5.0 ± 5.5; the p-value for the difference in HAM-D score between investigated groups at 12th week was p = 0.93, deeming it statistically insignificant.

Nevertheless, the authors reported that the last dose of escitalopram was higher in the placebo group than in the intervention group by 4.2 mg per day, which may implicate that supplementing vitamin D during pharmacotherapy of depression may lead to administering lower doses of antidepressants. However, researchers emphasized that this phenomenon needs to be further studied. No serious adverse events occurred in the intervention group; 4 participants withdrew because of the adverse effects in the placebo group. Hansen et al., (2019) in their trial administered orally 2800 IU of vitamin D daily for 12 weeks as an intervention to patients suffering from mild to severe depression. 62 patients were included in the trial, but 45 completed the full follow-up in the 6th month; patients received appropriate education and pharmacotherapy.

The mean age of the intervention group was 39.6 ± 13.5 years, and the control group was 38.7 ± 11.4 years (the mean age of all participants was 39.1 ± 12.3 years). Mean vitamin D plasma concentration in the intervention group at the baseline was 17.3 ± 9.8 ng/ml vs 39.2 ± 10.0 ng/ml in 6th month; in the placebo group at the baseline 17.7 ± 9.6 ng/ml vs 20.8 ± 13.4 ng/ml at 6th month follow-up. The

baseline HAM-D scores for the intervention and control group were 18.4 ± 5.73 and 18.0 ± 6.01, respectively. At the 6th month follow-up, they decreased in the intervention and control groups to 9.26 ± 6.32 and 9.59 ± 7.82, respectively, with p-value = 0.17. The authors reported that the intervention did not cause a significant reduction in the HAM-D scores between the investigated groups. Furthermore, researchers stated that no side effects were related to vitamin D intervention.

Torrisi et al., (2021) investigated the effect of daily supplementing for 12 weeks of 2,000 IU of vitamin D in poststroke patients undergoing intensive neurorehabilitation. Patients enrolled were not using antidepressant medications or vitamin D supplementation, and an experimental group comprised 40 patients. The mean age of the participants in the intervention group was 59.20 ± 11.38 years and 62.07 ± 10.82 years for the control group; this trial had significantly older patients than most of the trials we included in our review, but the mean age was still within the range we set in inclusion criteria. Surprisingly, vitamin D plasma concentration increased both in the intervention group and control group, from 19.62 ± 7.92 ng/ml to 30.65 ± 6.36 ng/ml and from 14.05 ± 4.9 ng/ml to 30.31 ± 4.03 ng/ml, respectively.

MADRS score in the intervention group decreased from 22.13 ± 6.68 to 9.73 ± 4.7 and in the control group from 21.86 ± 10.43 to 16.36 ± 11.63 with p-value = 0.06 for the difference in MADRS scores at the end of the study between the intervention and the control groups. The authors stated that vitamin D supplementation was not deemed effective as the improvement in psychological aspects occurred both in the intervention and control group; the difference in MADRAS decrease was greater in the intervention group, but the p-value was 0.06, deeming it statistically insignificant. The authors stated that the decrease in depression severity in both groups was probably linked to intensive rehabilitation. Researchers did not provide data on whether any adverse events occurred.

4. DISCUSSION

Our review screened 745 articles, including 10 in the final analysis. Five supported the positive effect of supplementing vitamin D in vitamin D deficient and insufficient patients with depression severity. Five reported no statistically significant difference between the groups supplementing vitamin D and the control groups. Our findings imply that this area needs further research. Furthermore, different approaches to this matter should be considered. As was described earlier, UVB radiation is vital for vitamin D synthesis in humans; it is estimated that sun exposure from 5 to 30 minutes per day without sunscreen may suffice in the daily production of vitamin D Srivastava, (2021); hence, other interventions than supplementing vitamin D should be considered and investigated. In the study by Thomas and Al-Anouti, (2018), the researchers used Sun Exposure and Behavioral Activation (SEBA) instead of supplementing vitamin D.

As the authors explain, SEBA uses the basis of cognitive behavioral therapy (CBT) and behavioral activation combined with daytime outdoor activities. The vitamin D serum levels at baseline were 4.2 ± 2.2 ng/ml for the intervention group and 4.4 ± 2.5 ng/ml for the control group. Through the intervention, vitamin D serum levels increased in the intervention group to 7.8 ± 4.7 ng/ml, whereas in the control group, they were 3.6 ± 2.0 ng/ml with p-values of the difference between values after the intervention p = 0.003. The mean BDI-II scores for the intervention and control groups were 23.8 ± 10.68 and 23.3 ± 9.06, respectively. After the intervention, the mean BDI-II scores were 13.1 ± 6.26 for the intervention and 22.8 ± 10.96 for the control group; with a p-value of 0.01, deeming this difference statistically significant.

This shows that other interventions than directly supplementing vitamin D or combined with it may be beneficial for patients suffering from depression. Moreover, it is crucial to consider that even if vitamin D by itself cannot improve depression severity, maybe it can lead to administering lower doses of antidepressants, as was shown in the study by Kumar et al., (2022), thus, leading to a lower rate of adverse effects and improving compliance. In the studies we described, no serious adverse events occurred when supplementing vitamin D; hence, this intervention seems to be safe for many patients.

Limitations

The first and foremost limitation of the studies we explored is that they enrolled a relatively small number of patients, most of the investigated groups were below 100 participants, and only one of them had more than 100 participants. It is vital that further studies involve a greater number of patients. Moreover, it is difficult to compare changes in depression severity, as in the ten articles we investigated, five different standardized depression rating scales were used.

Furthermore, in some studies, patients either did not reach the threshold of vitamin D serum levels defining vitamin D sufficiency or vitamin D serum levels were not measured after the intervention; hence, we have no way of knowing if reaching that threshold would further improve or not their depression severity. Vitamin D was supplemented using different routes, different doses, and over different periods; this could be one of the causes of the varied outcomes of the articles we described. Another limitation is that we only screen the PubMed database for eligible articles. Although it contains many articles from various journals, it is advised that in the following reviews, other databases, such as Google Scholar or the Cochrane Library, should be investigated.

5. CONCLUSIONS

Drawing upon our findings, the literature remains divided about the effect of supplementing vitamin D on depression severity in vitamin D deficient and insufficient patients. Half of the articles we included in our research were in favor of the positive relationship, and half of them reported no statistically significant difference between the intervention and the control groups. Our analysis shows that further research needs to be conducted as it is hard to draw clinical implications based on the equivocal data in the presented articles.

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Author's Contributions

Marcin Głód: Conceptualization; methodology; investigation; data curation; writing - rough preparation; supervision; project administration.

Kinga Filipek: Software; resources; writing - rough preparation; visualization.

Hanna Behrendt: Investigation; writing - rough preparation; writing - review and editing; visualization.

Agata Pisklak: Formal analysis; resources; writing - review and editing.

Marta Węgrzynek: Software; formal analysis; data curation; writing - rough preparation.

Ethical approval

Not applicable.

Informed Consent

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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